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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,039	02/08/2002	Makoto Kikuchi	06501-026002	3631

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FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,039	KIKUCHI ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-24,27 and 28* is/are rejected.

7)☒ Claim(s) *25-26 and 29-30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/214,569.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/8/03; 10/1/03; 2/8/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 08 February 2002 has been entered in full. Claims 1-20 are cancelled and claims 21-30 are added. It is noted that Applicant has requested a corrected filing receipt in the communication of 12 August 2002. Such will be mailed after this communication.

Claims 21-30 are under consideration in the instant application.

Information Disclosure Statement

The information disclosure statement filed 08 February 2002 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. Specifically, the English translation of the Bessho reference has not been submitted.

Specification

1. The disclosure is objected to because of the following informalities:

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "EXPANSION OF HEMATOPOIETIC CELLS USING MIDKINE OR PLEIOTROPHIN".

3. The Brief Description of Drawings does not refer to Figures 2A-2B or 3A-3B.

Appropriate correction is required.

Claim Objections

4. Claims 25-26 and 29-30 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 21-24, 27-28 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method for promoting *ex vivo* expansion of hematopoietic stem cells or hematopoietic progenitor cells comprising culturing the hematopoietic stem cells or progenitor cells with a composition comprising: (a) purified midkine (MK) protein or pleiotrophin (PTN) protein; and (b) one or more other purified hematopoietic growth factors selected from the group consisting of interleukin-3 (IL-3), interleukin-6 (IL-6), granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), stem cell factor (SCF), and erythropoietin (EPO), *does not* reasonably provide enablement for a method for promoting *ex vivo* expansion of hematopoietic stem cells or hematopoietic progenitor cells comprising culturing the hematopoietic stem cells or progenitor cells with a composition comprising: (a) purified midkine protein or PTN protein; and (b) one or more other purified hematopoietic growth factors. The specification is also enabling for a method for promoting *ex vivo* expansion of hematopoietic stem cells or hematopoietic progenitor cells comprising culturing the hematopoietic stem cells or progenitor cells with a composition

comprising: (a) purified midkine protein; and (b) one or more other purified hematopoietic growth factors selected from the group consisting of interleukin-3 (IL-3), interleukin-6 (IL-6), stem cell factor (SCF), and erythropoietin (EPO), *but the specification does not* reasonably provide enablement for a method for promoting *ex vivo* expansion of hematopoietic stem cells or hematopoietic progenitor cells comprising culturing the hematopoietic stem cells or progenitor cells with a composition comprising: (a) purified midkine protein; and (b) one or more other purified hematopoietic growth factors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method for promoting *ex vivo* expansion of hematopoietic stem cells or hematopoietic progenitor cells comprising culturing the hematopoietic stem cells or progenitor cells with a composition comprising: (a) purified midkine protein or PTN protein; and (b) one or more other purified hematopoietic growth factors. The claims also recite a method for promoting *ex vivo* expansion of hematopoietic stem cells or hematopoietic progenitor cells comprising culturing the hematopoietic stem cells or progenitor cells with a composition comprising: (a) purified midkine protein; and (b) one or more other purified hematopoietic growth factors. The claims recite that the hematopoietic stem cells or progenitor cells are obtained from bone marrow, peripheral blood, or umbilical cord blood. The claims recite that the hematopoietic stem cells are colony-forming-units-mix (CFU-mix). Additionally, the claims recite that one or more other purified hematopoietic growth factors selected from the group consisting of interleukin-3 (IL-3), interleukin-6 (IL-6), granulocyte colony stimulating factor (G-

CSF), granulocyte macrophage colony stimulating factor (GM-CSF), stem cell factor (SCF), and erythropoietin (EPO).

The specification of the instant application teaches that MK "exerts an extremely remarkable synergistic effect for proliferating and differentiating hematopoietic cells when used together with SCF, M-CSF, G-CSF, GM-CSF, IL-3, and IL-6" (pg 4, lines 17-20; Figures 1-3, especially). The specification also discloses that PTN alone exhibits the colony-forming capability like MK and the number of colonies formed is high (pg 12, lines 24-25). The specification indicates that a synergistic action of PTN with G-CSF to promote the colony formation is similarly observed as in the case of MK (pg 12, lines 26-2; Figure 11). However, the specification of the instant application does not teach any methods or working examples that promote *ex vivo* expansion of hematopoietic stem cells or progenitor cells with a composition comprising MK or PTN and all possible combinations of other purified hematopoietic growth factors. Undue experimentation would be required by one skilled in the art to determine if all hematopoietic and combinations thereof would have the desired biological effect when combined with MK or PTN. Extensive combinations of growth factors would have to be tested, even if, for example, there were 25-30 growth factors known at the time the invention was made. Each growth factor would have to be tested one at a time with other growth factors and then in groups and eventually with MK or PTN. For example, Brugger et al. (Blood 81: 2579-2584, 1993) only tests 10 different growth factors and uses 36 combinations of these factors to determine their ability to expand the number of clonogenic peripheral blood progenitor cells. Further, the specification of the instant application provides little or no guidance for directing one skilled in the art as to how to proceed with testing all possible combinations. Additionally, the state of the

art at the time the invention was made was such that midkine and pleiotrophin were characterized as heparin binding proteins which also enhanced neurite outgrowth and/or the survival of neurons (Backer et al., U.S. Patent 5,461,029, col 2, lines 44-46; Muramatsu, T., Develop Growth & Diff 36(1): 1-8, 1994, especially pg 1 and pg 3 bottom of col 2 through pg 4). The state of the art also teaches that MK and pleiotrophin (also known as HBNF and HB-GAM) enhance the plasminogen activator in endothelial cells and inhibit the infectivity of Herpesviridae virus and human cytomegalovirus (HCMV) (Kojima et al., Biochem Biophys Res Comm 216(2): 574-581, 1995; Backer et al., U.S. Patent 5,461;029; col 10). Therefore, the results of the instant specification that indicate MK and PTN promote the *ex vivo* expansion of hematopoietic stem and progenitor cells are unexpected over the prior art. One skilled in the art would not be able to predict that culturing all possible hematopoietic factors with MK or PTN would promote *ex vivo* expansion of hematopoietic stem or progenitor cells.

Due to the large quantity of experimentation necessary to determine which hematopoietic growth factors encompassed by the claims would promote hematopoietic stem cell and hematopoietic progenitor cell expansion *ex vivo* when co-administered with MK or PTN, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the breadth of the claims which fail to limit the growth factors, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Emerson et al. U.S. Patent 5,399,493 (expansion of hematopoietic stem and progenitor cells in culture using cytokines)

Hoffman et al. U.S. Patent 5,409,825 (expansion of hematopoietic stem and progenitor cells in culture using mast cell growth factor, IL-3, GM-CSF)

Emerson et al. U.S. Patent 5,437,994 (expansion of hematopoietic stem and progenitor cells in culture using cytokines)

WO 95/09640 (expansion of hematopoietic stem and progenitor cells in culture using cytokines and stromal cells)

Szilvassy, S. Ach Med Res 34 : 446-460, 2003 (review of hematopoietic stem and progenitor cells, including where they can be located)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BEB
Art Unit 1647
29 September 2004

Bridget E. Bunner